ClinicalEvidence

Trachoma

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ABSTRACT

INTRODUCTION: Active trachoma is caused by chronic infection of the conjunctiva by Chlamydia trachomatis, and is the world's leading infectious cause of blindness. Infection can lead to: scarring of the tarsal conjunctiva; inversion of the eyelashes (trichiasis), so that they abrade the cornea; and corneal opacity, resulting in blindness. Trachoma is a disease of poverty, overcrowding, and poor sanitation. Active disease affects mainly children, but adults are at increased risk of scarring. METHODS AND OUTCOMES: We conducted a systematic overview, aiming to answer the following clinical question: What are the effects of interventions to prevent scarring trachoma by reducing the prevalence of active trachoma? We searched: Medline, Embase, The Cochrane Library and other important databases up to December 2014 (BMJ Clinical Evidence overviews are updated periodically; please check our website for the most up-to-date version of this overview). RESULTS: At this update, searching of electronic databases retrieved 170 studies. After deduplication and removal of conference abstracts, 96 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 61 studies and the further review of 35 full publications. Of the 35 full articles evaluated, three previously included systematic reviews were updated, one systematic review and two RCTs were added at this update, and two RCTs and one further report were added the Comment sections. We performed a GRADE evaluation for nine PICO combinations. CONCLUSIONS: In this systematic overview, we categorised the efficacy for seven interventions based on information about the effectiveness and safety of antibiotics, face washing (alone or plus topical tetracycline), fly control (through the provision of pit latrines, and using insecticide alone or plus antibiotics), and health education.

QUESTIONS

INTERVENTIONS

Key points

- Active trachoma is caused by chronic infection of the conjunctiva by *Chlamydia trachomatis*, and is the world's leading infectious cause of blindness.

  Infection can lead to scarring of the tarsal conjunctiva, shortening and inversion of the upper eye lid (entropion), and scarring of the eye by the inverted eyelashes (trichiasis), resulting in blindness.

  Trachoma is a disease of poverty, overcrowding, and poor sanitation. Active disease mainly affects children, but adults, particularly women, are at increased risk of scarring.

- In previous versions of this overview, we included an evaluation of the evidence for effects of eye lid surgery for treating entropion and triachiasis. However, in this update, we have instead have focused on other selected interventions to help answer the clinical question: What are the effects of interventions to prevent scarring trachoma by reducing the prevalence of active trachoma?

- We searched for evidence on the effectiveness of selected interventions in trachoma from RCTs and systematic reviews of RCTs.

  We found few high-quality RCTs, and few RCTs on the effects of many of the interventions we examined.

  There is a need for further studies. However, the difficulties of undertaking RCTs in this field should not be underestimated.

- Public health interventions to improve hygiene may reduce the risks of developing trachoma, but studies have given conflicting results.

- Face washing plus topical antibiotics may be beneficial, but we don't know whether face washing alone is effective.

  Face washing is not always well defined to indicate if face cleanliness is actually achieved. Face cleanliness is the key element in terms of prevention of transmission.

- Fly control using insecticide alone or insecticide plus mass antibiotics, or by providing pit latrines, may reduce the risks of trachoma, but is unlikely to be a feasible large-scale approach.

- The systematic review we found evaluating antibiotics for trachoma pooled data on both oral and topical formulations. Antibiotics (oral and topical combined) may be more effective than control at reducing trachoma at 3 and 12 months. However, evidence was weak, and the RCTs were heterogeneous. Almost all RCTs in individuals were undertaken in children, and the generalisability of findings from these RCTs to adults is uncertain.

We don't know whether oral and topical antibiotics differ in effectiveness at reducing trachoma at 3 and 12 months as we found inconsistent evidence.

Clinical context

GENERAL BACKGROUND

Although trachoma has been controlled in many areas, it is still responsible for 1% of blindness and visual impairment worldwide, according to data from the Global Burden of Disease (GBD) study and the World Health Organisation (WHO). Therefore, it is extremely important to carefully weigh the evidence of interventions that will prevent recurrent infections and frame them in a cost-efficient way, so that authorities can properly invest in an era of many competing health priorities.

FOCUS OF THE REVIEW

In previous versions of this overview, we included an evaluation of the evidence for effects of eye lid surgery for treating entropion and triachiasis. However, in this update, we instead have focused on other selected interventions to help answer the clinical question: What are the effects of interventions to prevent scarring trachoma by reducing the prevalence of active trachoma?

COMMENTS ON EVIDENCE

A number of very well-conducted studies have been added to the pool of knowledge since the last update of this overview for the clinical question: What are the effects of interventions to prevent scarring trachoma by reducing the prevalence of active trachoma? This is particularly the case with respect to the use of antibiotics. Clinical questions concerning antibiotics for trachoma that remain less than adequately answered include: How long should mass distribution of antibiotics continue when hypoendemic levels have been reached? How should antibiotics be distributed (i.e., should it just be a matter of targeted distribution)? General difficulties with research and evaluation of the evidence in this field include the paucity of high-quality RCTs, particularly those that include sanitation and hygiene interventions, different diagnostic criteria and outcome measures used, the lack of a standard to define a clean face, the frequent difficulty in monitoring progression from scarring to trichiasis and, hence, to corneal opacity in large populations, and the applicability of data from specific communities to other communities in different settings.

SEARCH AND APPRAISAL SUMMARY

The update literature search for this overview was carried out from the date of the last search, January 2007, to December 2014. For more information on the electronic databases searched and criteria applied during assessment of studies for potential relevance to the overview, please see the Methods section. Searching of electronic databases retrieved 170 studies. After deduplication and removal of conference abstracts, 96 records were screened for inclusion in the overview. Appraisal of titles and abstracts led to the exclusion of 61 studies and the further review of 35 full publications. Of the 35 full articles evaluated, three previously included systematic reviews were updated, one systematic review and two RCTs were added at this update, and two RCTs and one further report were added the Comment sections.

ADDITIONAL INFORMATION

There is evidence for a strong association between trachomatous trichiasis and relative poverty, lending further evidence that general improvements and successful implementation of the SAFE strategy (a set of four interventions recommended by WHO in order to eliminate blinding trachoma as a public health problem) might improve both health and wealth of individuals and communities. The SAFE strategy has been implemented as part of trachoma control policies all over the world. Mathematical models have been developed to analyse the impact of each of the components of the SAFE strategy on disease sequelae. [1]

DEFINITION

Active trachoma is chronic inflammation of the conjunctiva caused by infection with *Chlamydia trachomatis*. The World Health Organization (WHO) simplified trachoma grading scheme defines active trachoma as trachomatous inflammation-follicular (TF) and/or trachomatous inflammation-intense (TI), where TF is the presence of five or more follicles in the central part of the upper tarsal conjunctiva, each at least 0.5 mm in diameter, and TI is pronounced inflammatory thickening of the upper tarsal conjunctiva that obscures more than half of the normal deep vessels. [2] **Cicatricial trachoma** is caused by repeated infection with *C trachomatis*; it includes the presence of visible scars on the tarsal conjunctiva (trachomatous scarring [TS]), shortening and inversion of the upper eye lid (entropion), and malposition of the lashes so that they abrade the eye (trachomatous trichiasis [TT]). Trachomatous scarring can be present without entropion/trichiasis, but if entropion/trichiasis is present because of trachoma, there will be scarring. Trachoma blindness results from corneal opacification (CO), which occurs because of the mechanical trauma wrought by entropion/trichiasis. **Diagnosis** of trachoma is by clinical examination, using the criteria set out in either

the modified WHO grading system [3] or the WHO simplified grading system. [2] The simplified grading system is now the most commonly employed.

INCIDENCE/ PREVALENCE

Trachoma is the world's leading cause of infectious blindness. [4] Globally, about 232 million people live in trachoma-endemic areas and need treatment. An estimated 7.2 million people have trachomatous trichiasis. [5] Trachoma is a disease of poverty, regardless of geographical region. Cicatricial trachoma is prevalent in large regions of Africa, the Middle East, Asia, and Aboriginal communities in Australia, and there are also small foci in Central and South America. [4] [6] In areas where trachoma is constantly present at high prevalence, active disease may be found in more than 50% of pre-school children, and may have a prevalence as high as 60% to 90%, [7] and as many as 75% of women and 50% of men aged over 45 years may show signs of scarring disease. [8] The prevalence of active trachoma decreases with increasing age. [7] Although similar prevalences of active disease are observed in young boys and girls, the later sequelae of trichiasis, entropion, and corneal opacification are usually more common in women than men. [7]

AETIOLOGY/ RISK FACTORS

Active trachoma is associated with poor hygiene, youth, poor access to water and sanitation, and close contact between people. Infected eye and nasal secretions are the mode of transmission of ocular *C trachomatis* infection, which is why having a clean face is so important. [9] Sharing a bedroom (particularly sharing a bed) with someone who has active trachoma is a risk factor for infection. [10] The density of eye-seeking flies in a community is associated with active trachoma. [11] [12] Flies important to trachoma transmission lay their eggs on human faeces lying exposed on the soil, which suggests that access to improved sanitation might help control trachoma. [13] [14] The SAFE strategy is a set of four interventions recommended by WHO in order to eliminate blinding trachoma as a public health problem. Each letter of the word SAFE represents part of the strategy as follows: Surgery (for trichiasis); Antibiotics; Facial cleanliness; Environmental improvement. [15] One study demonstrated a strong association between trachomatous trichiasis and relative poverty, lending further evidence that general improvements and successful implementation of the SAFE strategy might improve both health and wealth of individuals and communities. [16]

PROGNOSIS

Corneal damage from trachoma is caused by multiple processes. Scarring trachoma damages glandular structures and may cause an inadequate tear film; a dry eye may be more susceptible to damage from inturned lashes and superadded infection by other bacteria and fungi, leading to corneal opacification.

AIMS OF INTERVENTION

To prevent ongoing transmission of infection, and so prevent or cure active trachoma; to reduce the rate of progression to scarring trachoma, with minimal adverse effects.

OUTCOMES

Prevalence of active trachoma (laboratory evidence of *C trachomatis* infection); **adverse effects**. We have reported the presence of active trachoma in preference to laboratory evidence of *C trachomatis* infection. However, we have reported the laboratory evidence of *C trachomatis* infection on occasion where active trachoma has been sparsely reported, in order to augment reporting. RCTs conducted before 1981 may use definitions of trachoma that differ from the present simplified WHO definitions. [2] [3]

METHODS

Search strategy *BMJ Clinical Evidence* search and appraisal date December 2014. Databases used to identify studies for this systematic overview include: Medline 1966 to December 2014, Embase 1980 to December 2014, The Cochrane Database of Systematic Reviews 2014, issue 12 (1966 to date of issue), the Database of Abstracts of Reviews of Effects (DARE), and the Health Technology Assessment (HTA) database. **Inclusion criteria** Study design criteria for inclusion in this systematic overview were systematic reviews and RCTs published in English, at least single-blinded, and containing more than 20 individuals (with at least 10 people per intervention arm), of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. *BMJ Clinical Evidence* does not necessarily report every study found (e.g., every systematic review). Rather, we report the most recent, relevant, and comprehensive studies identified through an agreed process involving our evidence team, editorial team, and expert contributors. **Evidence evaluation** A systematic literature search was conducted by our evidence team, who then assessed titles and abstracts, and finally selected articles for full text appraisal against inclusion and exclusion criteria agreed *a priori* with our expert contributor. In consultation with the expert contributor, studies were selected for inclusion and all data relevant to this overview extracted into the benefits and harms section of the overview. In addition, information that did not meet our pre-defined criteria for inclusion in the benefits and harms section may have been reported in the 'Further information on studies' or 'Comment' section (see below). **Adverse effects** All serious adverse effects, or those adverse effects reported as statistically significant, were included in the harms section of the overview. Pre-specified adverse effects identified as being clinically important were also reported,

even if the results were not statistically significant. Although *BMJ Clinical Evidence* presents data on selected adverse effects reported in included studies, it is not meant to be, and cannot be, a comprehensive list of all adverse effects, contraindications, or interactions of included drugs or interventions. A reliable national or local drug database must be consulted for this information. **Comment and Clinical guide sections** In the Comment section of each intervention, our expert contributor may have provided additional comment and analysis of the evidence, which may include additional studies (over and above those identified via our systematic search) by way of background data or supporting information. As *BMJ Clinical Evidence* does not systematically search for studies reported in the Comment section, we cannot guarantee the completeness of the studies listed there or the robustness of methods. Our expert contributors add clinical context and interpretation to the Clinical guide sections where appropriate. **Structural changes this update** At this update, we have removed the following previously reported question: What are the effects of eye lid surgery for treating entropion and trichiasis? **Data and quality** To aid readability of the numerical data in our overviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). *BMJ Clinical Evidence* does not report all methodological details of included studies. Rather, it reports by exception any methodological issue or more general issue that may affect the weight a reader may put on an individual study, or the generalisability of the result. These issues may be reflected in the overall GRADE analysis. We have performed a GRADE evaluation of the quality of evidence for interventions included in this overview (see table, p 14). The categorisation of the evidence (high, moderate, low, very low) reflects the quality of the evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *BMJ Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. Further details of how we perform the GRADE evaluation and the scoring system we use can be found on our website (www.clinicalevidence.com).

QUESTION **What are the effects of interventions to prevent scarring trachoma by reducing the prevalence of active trachoma?**

OPTION ANTIBIOTICS

Prevalence of trachoma

Antibiotics compared with placebo or no treatment Antibiotics (oral and topical combined in the analysis) may be more effective than placebo or no treatment at reducing trachoma at 3 and 12 months. However, evidence was weak, the RCTs were heterogeneous, almost all RCTs in individuals were undertaken in children, and the generalisability of findings from these RCTs to adults is uncertain (very low-quality evidence).

Oral antibiotics compared with topical antibiotics We don't know whether oral and topical antibiotics differ in effectiveness at reducing trachoma at 3 and 12 months, as we found inconsistent evidence (very low-quality evidence).

For GRADE evaluation of interventions for trachoma, see table, p 14 .

Benefits:

We found two systematic reviews. [17] [18] The first review (search date 2010) examined the effects of antibiotics and pooled data. [17] The second review (search date 2013) examined the added effects of water, sanitation, and hygiene education on mass drug administration. [18] The second review found no RCTs of sufficient quality. We excluded one further RCT [19] identified by the second systematic review [18] because the randomisation schedule was broken. We have therefore reported the first review in detail. [17] The first review separately examined data for randomised trials involving individuals and cluster-randomised trials of communities, and we have reported both analyses below. It included RCTs of oral or topical antibiotic treatment, and included further unpublished data from the original trial authors. The review noted that almost all RCTs in individuals were undertaken in children, and that the generalisability of these results to adults was uncertain. [17] In the community RCTs, adults and children were included, but because of the small number of trials included, the review reported that it was not possible to determine if effects were different between adults and children.

Antibiotics versus placebo or no treatment:

In considering RCTs that examined individual treatment, the review found that antibiotics significantly reduced active trachoma at 3 months and the result was of borderline significance at 12 months (3 months: 9 RCTs, 813/1296 [63%] with antibiotics *v* 517/665 [78%] with control [placebo or no treatment], RR 0.78, 95% CI 0.69 to 0.89, P = 0.00014; 12 months: 4 RCTs, 400/719 [56%] with antibiotic *v* 231/316 [73%] with control, RR 0.74, 95% CI 0.55 to 1.00, P = 0.050). [17] However, there was significant heterogeneity in both analyses (3 months: I^2 = 73%, P for heterogeneity = 0.00027; 12 months: I^2 = 90%, P for heterogeneity <0.00001). The review noted that one

source of potential heterogeneity was whether oral or topical antibiotics had been used, and analysed these subgroups on this basis. The review found that oral antibiotics significantly reduced trachoma at 3 months but not at 12 months (3 months: 6 RCTs, 599 people, RR 0.81, 95% CI 0.67 to 0.97, P = 0.024; 12 months: 3 RCTs, 429 people, RR 0.87, 95% CI 0.76 to 1.00, P = 0.057). However, both results were significantly heterogeneous (3 months: I^2 = 60%, P for heterogeneity 0.03; 12 months, I^2 = 89%, P for heterogeneity = 0.00015). The review found that topical antibiotics significantly reduced trachoma at 3 and 12 months (3 months: 6 RCTs, 1478 people, RR 0.82, 95% CI 0.72 to 0.92, P = 0.00097; 12 months: 4 RCTs, 724 people, RR 0.79, 95% CI 0.71 to 0.88, P = 0.000015). However, the result at 3 months was significantly heterogeneous (3 months: I^2 = 68%, P for heterogeneity 0.01; 12 months, I^2 = 46%, P for heterogeneity = 0.13). [17] The review noted that such subgroup analysis could be misleading, as there may have been further differences between trials other than the type of antibiotic used (see Comment, p 4), and the subgroup analysis was not pre-specified.

In considering community-based RCTs, two RCTs examined the effects of azithromycin. [17] One RCT found a significantly reduced risk of trachoma with antibiotics at 12 months (258/634 [41%] with oral azithromycin *v* 429/613 [70%] with control [placebo or no treatment], RR 0.58, 95% CI 0.52 to 0.65), while another RCT found a non-significant increase in risk with antibiotics (21/523 [4.0%] with oral azithromycin *v* 35/993 [3.5%] with control, RR 1.14, 95% CI 0.67 to 1.94), and the review noted that it was difficult to explain these differences. [17] The review also found significantly less *C trachomatis* infection with oral azithromycin compared with control at 12 months (4 RCTs, 4345 people), but there was significant heterogeneity in the analysis (I^2 = 85%, P for heterogeneity 0.00017), and the review noted that the size of the pooled effect was likely to be unreliable because of differences between studies. [17]

Oral antibiotics versus topical antibiotics:
In considering RCTs that examined individual treatment, the review found no significant difference between oral and topical antibiotic treatment in trachoma at 3 or 12 months (3 months: 6 RCTs, 310/538 [58%] with oral antibiotic *v* 245/415 [59%] with topical antibiotic, RR 0.98, 95% CI 0.82 to 1.18, P = 0.85; 12 months: 5 RCTs, 232/499 [47%] with oral antibiotic *v* 188/387 [49%] with topical antibiotic, RR 0.93, 95% CI 0.75 to 1.15, P = 0.52). However, the result at 3 months was significantly heterogeneous (I^2 = 63%, P for heterogeneity 0.02). Sensitivity analysis removing one clinically heterogeneous RCT that used an unsupervised treatment schedule did not change the significance of the results but reduced heterogeneity (3 months: 5 RCTs, RR 1.04, 95% CI 0.94 to 1.16; 12 months: 4 RCTs, RR 1.01, 95% CI 0.85 to 1.20). Three RCTs compared oral azithromycin with topical tetracycline at 3 months. Removing the clinically heterogeneous RCT from the analysis, the review found no significant difference between oral azithromycin and topical tetracycline in trachoma at 3 months (2 RCTs, 220 people, RR 1.01, 95% CI 0.80 to 1.28, P value not reported). [17] The review found that oral azithromycin significantly reduced active trachoma compared with topical tetracycline at 12 months (2 RCTs, 92/266 [35%] with azithromycin *v* 69/181 [38%] with topical tetracycline, RR 0.76, 95% CI 0.59 to 0.99, P = 0.038). However, this analysis included the clinically heterogeneous RCT.

In considering community-based RCTs, the review found one RCT (ACT trial) comparing oral azithromycin with topical tetracycline, which took place in three different countries and noted that there was considerable heterogeneity of effect by location. [17] At 3 months, for active trachoma, one location favoured oral azithromycin (Egypt, 1825 people, RR 0.52, 95% CI 0.43 to 0.64), one location favoured topical tetracycline (Tanzania, 2577 people, RR 1.16, 95% CI 1.00 to 1.36), and one location found no difference (Republic of the Gambia, 1600 people, RR 0.76, 95% CI 0.5 to 1.15). At 12 months for active trachoma, two locations favoured oral azithromycin (Egypt, 1941 people, RR 0.74, 95% CI 0.61 to 0.90; Gambia, 1197 people, RR 0.55, 95% CI 0.40 to 0.75), while one location favoured topical tetracycline (Tanzania, 2276 people, RR 1.19, 95% CI 1.02 to 1.40). The review did not pool data for all three locations. The review noted that these results were not robust to statistical correction for cluster effects, which resulted in confidence intervals including a relative risk of 1 (i.e., no difference) in Egypt and Gambia.

Harms: The review reported that 12 of the 22 included studies did not report on harms. [17] One RCT that systematically reported adverse effects (TANA) found that 96/671 (14%) people had adverse effects with azithromycin, most (72) being gastrointestinal. [17] The review reported that there were no reports of serious adverse effects with oral azithromycin or topical tetracycline. [17]

Comment: Antibiotics used in the included RCTs were often oral azithromycin and topical tetracycline, but also included topical oxytetracycline, topical tetracycline derivative (GS2989), topical terramycin, topical azithromycin, oral doxycycline, oral trisulfapyrimidines, oral sulfamethoxypyridazine, oral sulfadimethoxine, and topical sulfafurazole.

We found one further RCT that examined the effects of mass antibiotic distributions on herd protection, [20] and one RCT that reported on the effects of mass distribution of azithromycin on overall mortality. [21]

Methods
The review noted that, in general, trials were clinically and statistically heterogeneous and most had limitations in their design. [17] Sequence generation and allocation concealment were poorly described, with only one RCT adequately describing both. [17] Only five RCTs reported efforts to mask the assessment of active trachoma. Only three RCTs provided data so that incomplete outcome data were unlikely. Four of the cluster RCTs only randomised two communities to treatment or control, and one cluster RCT only randomised six communities. [17] Some cluster-randomised RCTs analysed data on an individual basis. The review noted that while the trials in the review provided some evidence that individuals benefit from antibiotic treatment, the quality of the trials made it difficult to estimate the size of the effect, and the overall quality of evidence was low.

Clinical guide
Clinical questions concerning antibiotics that remain inadequately answered include: How long should mass distribution of antibiotics continue when hypoendemic levels have been reached? How should antibiotics be distributed (i.e., should it just be a matter of targeted distribution)? [22] [23] [24] [25] [26]

OPTION FACE WASHING ALONE

Prevalence of trachoma
Face washing compared with no intervention Face washing alone may be no more effective than no face washing at reducing the prevalence of trachoma in Aboriginal Australian children at 3 months, but we don't know about longer term. Evidence was limited and it is not clear if face washing actually indicated face cleanliness, which is the aim of the intervention (low-quality evidence).

For GRADE evaluation of interventions for trachoma, see table, p 14 .

Benefits:

Face washing versus no intervention:
We found one systematic review (search date 2011) [27] on the effect of face-washing promotion, which identified one RCT (reported in 2 publications). [28] [29] We have reported the RCT directly from its original reports. The RCT (1143 children in 36 Aboriginal communities in the Northern Territory of Australia) compared four groups: daily face washing alone, daily face washing plus daily topical tetracycline (as drops for 1 week each month), topical tetracycline alone, and no intervention. [28] [29] The RCT found no significant difference in the proportion of children with trachoma after 3 months between face washing alone and no intervention (191/246 [78%] with face washing alone *v* 160/211 [76%] with no intervention; regression analysis, P >0.05). [28] [29] Face washing was performed by a teacher for 3 months. Trachoma was defined as the presence of at least one follicle or some papillae on the upper tarsal plate (this study pre-dated publication of the present World Health Organization [WHO] trachoma grading schemes; see Comment, p 6). All of the children recruited to the trial had signs of trachoma at baseline according to this definition. Losses to follow-up were included in the analysis as being trachoma positive. The review obtained further details from the original RCT authors. It reported that it was unclear whether the baseline prevalence of trachoma was similar among the comparison groups and, although the RCT was of cluster design, the data were analysed at an individual level. [27]

Harms:

The systematic review gave no information about harms. [27]

Comment:

That fact that the RCT did not use the current WHO trachoma grading scheme to define its outcome measures may limit the applicability of its results. [28] [29] The review noted that the intervention was administered for only 3 months and it was unclear whether this time period was enough to demonstrate the impact of the intervention, and face washing was applied to children with already established disease rather than the whole population at risk. [27] The review [27] was updated shortly after the search date of this *BMJ Clinical Evidence* overview (to search date 2015). However, no additional RCTs were found.

Clinical guide
RCTs on face washing do not always clearly indicate if face cleanliness was actually achieved. Clean faces are the key element in preventing transmission as described in the SAFE strategy, a set of four interventions recommended by WHO in order to eliminate blinding trachoma as a public health problem. [15] One study in Australia evaluated current policies to prevent and treat trachoma in Aboriginal Australian communities, and simulated models for strategies where priorities for different interventions were shifted from the current strategy. The study projections showed an increased likelihood of controlling trachoma to less than 5% in 5- to 9-year-old children in hyperen-

demic communities by 2020 when facial cleanliness in children in communities where trachoma is hyperendemic was prioritised on a large scale compared with the current policy (from 31% with the current policy to 64% with the strategy shift). The most effective model of interventions included large-scale antibiotic distribution, screening, treatment, facial cleanliness, and housing construction targets. [30] A systematic review of 86 studies that measured effects of water, sanitation, and hygiene (WASH)-related interventions on trachoma outcomes (either active disease with clinical signs of trachomatous inflammation or infection diagnosed by PCR) performed 15 meta-analyses on different exposure-outcome pairs. It found that 'having a clean face' reduced the chance of trachomatous inflammation-follicular (TF) or trachomatous inflammation-intense (TI) (OR 0.42, 95% CI 0.32 to 0.52). Face washing was also found to significantly decrease the risk of TF or TI (face washing at least once daily: OR 0.76, 95% CI 0.57 to 0.96; face washing at least twice daily: OR 0.85, 95% CI 0.80 to 0.90). [31]

OPTION FACE WASHING PLUS ANTIBIOTICS

Prevalence of trachoma

Face washing plus topical tetracycline compared with no intervention Face washing plus topical tetracycline may be more effective than no face washing at reducing the prevalence of trachoma in Aboriginal Australian children at 3 months, but we don't know about longer term. Evidence was limited, and it is not clear if face washing actually indicated face cleanliness, which is the aim of the intervention (low-quality evidence).

Face washing plus topical tetracycline compared with topical tetracycline alone Promotion of face washing plus topical tetracycline may be more effective than topical tetracycline alone at reducing the risk of 'severe trachoma' at 1 year in children aged 1 to 7 years, but may be no more effective at reducing the risk of 'any trachoma' or the proportion of children with follicles compared with topical tetracycline alone (low-quality evidence).

For GRADE evaluation of interventions for trachoma, see table, p 14 .

Benefits:

Face washing plus topical tetracycline versus no intervention:
We found one systematic review (search date 2011) [27] on the effect of face-washing promotion, which identified one RCT (1143 children in 36 Aboriginal communities in the Northern Territory of Australia). [28] [29] We have reported the RCT directly from its original reports. The RCT compared four groups: daily face washing alone, daily face washing plus daily topical tetracycline (as drops for 1 week each month), topical tetracycline alone, and no intervention. [28] [29] It found that face washing plus tetracycline drops significantly reduced the proportion of children with trachoma after 3 months compared with no intervention (215/312 [69%] with face washing plus topical tetracycline *v* 160/211 [76%] with no intervention; regression analysis, P <0.05). [28] [29] Face washing was performed by a teacher for 3 months. Trachoma was defined as the presence of at least one follicle or some papillae on the upper tarsal plate (this study pre-dates publication of the present World Health Organization [WHO] trachoma grading schemes; see Comment, p 7). All of the children recruited to the trial had signs of trachoma at baseline according to this definition. Losses to follow-up were included in the analysis as being trachoma positive. The review obtained further details from the original RCT authors. It reported that it was unclear whether the baseline prevalence of trachoma was similar among the comparison groups and, although the RCT was of cluster design, the data were analysed at an individual level. [27]

Promotion of face washing plus topical tetracycline versus topical tetracycline alone:
We found one systematic review (search date 2011) [27] on the effect of face-washing promotion, which identified one cluster RCT (1417 children aged 1–7 years in 6 villages in Kongwa, Tanzania; see Comment, p 7 on cluster randomisation). [32] We have reported the RCT directly from its original report. The RCT compared 1 month's intensive promotion of face washing plus 30 days of daily topical tetracycline (ointment) with 30 days of daily topical tetracycline alone. [32] It found that promoting face washing plus topical tetracycline significantly reduced the risk of 'severe trachoma' after 1 year compared with topical tetracycline alone (OR for 'severe trachoma' 0.62, 95% CI 0.40 to 0.97). 'Severe trachoma' was defined, uniquely in the study, as the presence of 15 or more follicles, or the presence of inflammation that obscured all the deep tarsal vessels. It found that the reduction in risk of 'any trachoma' was not significant between groups (any trachoma, defined as follicular trachoma [TF] with or without inflammation: OR 0.81, 95% CI 0.42 to 1.59). [32] Although this combination did not find a significant reduction in the risk in TF, this was significant in trachomatous inflammation-intense (TI) cases. The RCT found that, when all participants from intervention and control villages were pooled, children who had a sustained clean face were significantly less likely to have 'any trachoma' than those who never had a clean face or who had a clean face at only one follow-up visit during the study period (OR 0.58, 95% CI 0.47 to 0.72). [32] The review also included one further four-armed RCT, [28] [29] which compared daily face washing plus daily topical tetracycline (as drops for 1 week each month) with topical tetracycline alone (see Face washing plus topical tetracycline versus no intervention, above). [27] The review found no significant difference

between the combination arm and the eye drops alone arm in the proportion of children with follicles at 3 months (215/312 [69%] with face washing plus topical tetracycline *v* 250/374 [67%] with topical tetracycline alone, RR 1.03, 95% CI 0.93 to 1.14). [27]

Harms: The review gave no information about harms. [27]

Comment: The fact that one RCT did not use the current WHO trachoma grading scheme to define their outcome measures may limit the applicability of their results. [28] [29] The review noted that, in the first RCT, [28] [29] the intervention was administered for only 3 months and that face washing was applied to children with already established disease rather than the whole population at risk. [27] Cluster randomisation in the second RCT comparing face washing plus topical tetracycline with topical tetracycline alone limits the power to detect differences between groups and the interpretation of results for individual children. [32]

Clinical guide
See Clinical guide for the option on Face washing alone, p 6 .

OPTION FLY CONTROL THROUGH THE PROVISION OF PIT LATRINES

Prevalence of trachoma
Fly control through the provision of household pit latrines compared with control Fly control through the provision of improved household pit latrines may be no more effective at reducing the prevalence of active trachoma compared with control (using existing facilities — mainly no or local latrines). Intensive latrine promotion plus a single treatment with antibiotics may be no more effective than a single treatment with antibiotics and no intensive latrine promotion at reducing the proportion of children aged 0 to 9 years with trachoma at 2 years (low-quality evidence).

For GRADE evaluation of interventions for trachoma, see table, p 14 .

Benefits: **Fly control through the provision of household pit latrines versus control:**
We found one systematic review (search date 2011) [33] on the effect of environmental sanitary interventions, which identified two RCTs. [12] [34] We have reported the RCTs directly from their original reports.

The first RCT compared seven sets of three village clusters (7080 people in 21 village clusters in Republic of the Gambia) with successive sets recruited 2 months apart to cover all different seasons. In each set of three village clusters, one cluster was randomised to receive household pit latrines, one to receive permethrin spraying, and one to receive no intervention (control). [12] Improved household pit latrines (non-ventilated) were provided on the basis of one per household or per 20 people — whichever allowed for the most latrines — whereas the control group used existing facilities (households: 97% with no latrine or local latrine). [12] The RCT found no significant difference in active trachoma prevalence between the provision of latrines and control (mean change compared with control clusters: –30%, 95% CI –81% to +22%; P = 0.210). [12]

The second cluster-randomised RCT in Ethiopia, which had six intervention arms in total, included two arms that compared a single treatment with antibiotics plus intensive latrine promotion (12 communities) with single treatment with antibiotics alone (12 communities). [34] Individuals aged 1 year and older received a single directly observed dose of oral azithromycin (or a 6-week course of topical tetracycline if <1 year old or pregnant) at baseline. Although 35,595 people (including 10,400 children aged 1–9 years) were included in the 24 communities at baseline, results were based on a random sample of 60 children aged 0 to 9 years from each community (24 communities, 1211 children in total). In the intensive latrine promotion arm, an existing latrine programme was intensified, heads of households were trained, there were multiple promotional visits, and cement slabs were offered, among other initiatives. The RCT reported on clinical signs of trachoma using the WHO simplified grading system (clinically active trachoma, grades TF and/or TI). It found no significant difference between latrine plus single antibiotic drug treatment and single antibiotic drug treatment alone in clinically active trachoma at 2 years (average: 46% with latrine plus single antibiotic treatment *v* 49% with single antibiotic treatment alone; P = 0.69). It also found no significant difference between groups in prevalence of ocular *C trachomatis* infection at 2 years (P = 0.93). [34] About 81% of households had a latrine in the latrine promotion group at 2 years compared with 30% in the single antibiotic treatment alone group (based on a survey of 240 households). There was a significant difference at baseline between the groups in the proportion of participants with antibiotic coverage in each group (95% with single antibiotic treatment alone *v* 89% with latrine plus single antibiotic treatment, P = 0.008). [34]

Harms: The review gave no information about harms. [33]

Comment: Cluster randomisation limits the power to detect differences between groups, and the interpretation of results for individuals. [12] [34] The review [33] noted that randomisation in the first RCT [12] was by drawing pieces of folded paper from a hat, and there was a high risk of bias with regard to blinding of participants and personnel for the evaluation of trachoma, and that there was unclear risk of bias with regard to blinding of outcome assessment in the second RCT. [34]

We found one further report [35] of one RCT, [34] which reported on mortality rather than trachoma outcomes.

Clinical guide
A systematic review of 86 studies that measured effects of water, sanitation, and hygiene (WASH)-related interventions on trachoma outcomes (either active disease with clinical signs of trachomatous inflammation or infection diagnosed by PCR) performed 15 meta-analyses on different exposure-outcome pairs. It found a reduced risk of TF or TI (OR: 0.85, 95% CI 0.75 to 0.95) and *C trachomatis* infection (OR 0.67, 95% CI 0.55 to 0.78) with access to sanitation. [31] For further results from this review, see Clinical Guide for the option on Face washing alone, p 6 .

A narrative review, published in 2013, considered the question of whether the SAFE strategy will be sufficient to eliminate trachoma by 2020, as is the current aim. [36] [37] One of the conclusions by the authors was that more research on the impact of environmental improvements on prevention is required. However, improvements in the environment are important in terms of improvement to the general health and hygiene of the community.

OPTION FLY CONTROL USING INSECTICIDE ALONE

Prevalence of trachoma
Fly control using insecticide compared with control Fly control using insecticides (deltamethrin and permethrin) may be more effective at reducing prevalence of active trachoma compared with control, but this short-term beneficial effect may be neither cost-effective nor environmentally acceptable on a large scale (low-quality evidence).

For GRADE evaluation of interventions for trachoma, see table, p 14 .

Benefits: **Fly control using insecticide versus no intervention:**
We found one systematic review (search date 2011) [33] on the effect of environmental sanitary interventions, which identified two RCTs. [11] [12] The first RCT identified by the review [33] was a pilot study comparing spraying of deltamethrin for 3 months with no intervention in two pairs of villages in Republic of the Gambia (any age, screened at 3 months: 484 people in 2 villages with intervention, 440 people in 2 villages with no intervention). [11] One pair of villages received deltamethrin or no intervention in the wet season, and the other pair received deltamethrin or no intervention in the dry season. The pilot study found that spraying of deltamethrin significantly reduced the number of new cases of trachoma (World Health Organization [WHO] classification) after 3 months compared with no intervention (wet and dry season combined, absolute numbers not reported; RR 0.25, 95% CI 0.09 to 0.64). [11] The second RCT identified by the review compared seven sets of three village clusters (7080 people in 21 village clusters in Gambia) with successive sets recruited 2 months apart to cover all different seasons. In each set of three village clusters, one cluster was randomised to receive permethrin spraying, one to receive household pit latrines, and one to receive no intervention (control). [12] The RCT found that permethrin spraying was associated with a significant reduction in the prevalence of active trachoma compared with control (mean change in village cluster prevalence compared with control clusters: –56%, 95% CI –19% to –93%; P = 0.01). [12]

Harms: **Fly control using insecticide versus no intervention:**
The review [33] reported on adverse effects from only one RCT. [11] It reported that the RCT found no adverse effects caused by deltamethrin spraying after 3 months' follow-up, but stated that it was not clear how this conclusion had been reached. [33]

Comment: Cluster randomisation limits the power to detect differences between groups, and the interpretation of results for individuals. [11] [12] The review did not pool data because of clinical heterogeneity between the two RCTs. One intervention was applied for 3 months, the other for 6 months, and it concluded that the RCTs must have been carried out at different seasons of the year (known to affect fly population and possibly transmission). [33] In the first included RCT, [11] the review noted that the allocation of the villages to each intervention was quasi-randomised, as the villages were said to be 'arbitrarily allocated'. [33] This RCT noted that fly control with insecticide was unlikely to be a sustainable routine public health measure in countries where trachoma prevalence is highest. [11] The second included RCT noted that long-term insecticide use as a control measure might lead to the evolution of insecticide resistance. [12] The review also noted that, although the two included RCTs found evidence of benefit with fly control using insecticide, the RCTs did not seem

to adequately assess the possibility of untoward effects from insecticide spraying over a prolonged period of time (years), and that the resources for community insecticide spray interventions are likely to be unsustainable for many poor trachoma-affected communities. [33] Hence, although the RCTs found evidence of a short-term benefit, it is unlikely that this intervention would be cost effective or acceptable (from an environmental point of view) were large-scale implementation attempted; the purpose of these trials was to demonstrate that fly-control interventions in general might be effective.

Clinical guide
Environmental improvements in general are more important than insecticide spraying, as the former will lead to sustainable changes that avoid breeding of flies, whereas insecticide spraying is just a temporary measure. (See Clinical Guide for the option on Fly control through provision of pit latrines, p 8 .)

OPTION FLY CONTROL USING INSECTICIDE PLUS MASS ANTIBIOTIC TREATMENT

We found no direct information from RCTs about the effects of insecticide plus mass antibiotic treatment on fly control.

For GRADE evaluation of interventions for trachoma, see table, p 14 .

Benefits: **Fly control using insecticide plus mass antibiotic treatment versus mass antibiotic treatment alone:**
We found one systematic review (search date 2011), which found no RCTs of sufficient quality (see Comment). [33]

Harms: **Fly control using insecticide plus mass antibiotic treatment versus mass antibiotic treatment alone:**
We found no RCTs.

Comment: The review included one RCT (302 children aged 1–7 years in 16 neighbourhoods in Kongwa, Tanzania) that compared insecticide spray (permethrin) plus azithromycin at baseline with no spray plus azithromycin at baseline. [33] However, loss to follow-up was higher than the minimum inclusion criteria for this *BMJ Clinical Evidence* review (over 30% at 1 year), so we have not reported the RCT further.

Clinical guide
Environmental improvements in general are more important than insecticide spraying, as the former will lead to sustainable changes that avoid breeding of flies, whereas insecticide spraying is just a temporary measure. (See Clinical Guide for the option on Fly control through provision of pit latrines, p 8 .)

OPTION HEALTH EDUCATION

Prevalence of trachoma
Health education compared with no intervention Health education may be more effective than no intervention at reducing the incidence of active trachoma at 6 months. However, evidence was weak (very low-quality evidence).

Health education plus improved water supply compared with no intervention We don't know whether health education plus improved water supply is more effective than no intervention at reducing trachoma in children aged 1 to 5 years old at 1 or 2 years (very low-quality evidence).

For GRADE evaluation of trachoma, see table, p 14 .

Benefits: **Health education versus no intervention:**
We found one systematic review (search date 2011) [33] on the effect of environmental sanitary interventions, which identified one RCT. In the RCT, four villages in Mali were randomised to receive either: mass topical tetracycline treatment plus a health-education programme; mass topical tetracycline treatment alone; a health-education programme alone; or no intervention (1810 people in 4 villages, all ages). [33] The health-education programme consisted of information on personal and family hygiene, including household sanitation, and information on trachoma and its complications. It included posters and booklets, and was conducted for 1 week per month for 6 months. [33] The review found that the incidence of active trachoma was significantly lower in the health-education-alone village than in the control village at 6 months (4% with health education *v* 7% with no intervention, odds of reducing trachoma with health education OR 2.4, 95% CI 1.1 to 5.1, absolute numbers not reported). [33] However, the review found it difficult to draw robust conclusions from the RCT because there was only one cluster (village) per arm, and it was difficult to determine

whether any differences were due to the intervention or due to inherent differences between the villages. [33] The review also noted that outcome assessment was not blinded, and the analysis may not have adequately allowed for differences in the unit of allocation and analysis. [33]

Health education plus improved water supply versus no intervention:
We found one systematic review (search date 2011), [33] which identified one RCT based in the Maradi district in West Africa. [38] The community-based cluster-randomised RCT examined 557 sentinel children aged 1 to 5 years old in six villages randomised to health education plus improved water supply versus six villages with no intervention. Data were only collected for 10 villages. The intervention villages had a 3-month health education programme prior to the 2-year survey and at least one clean water well constructed. The health education intervention included a dedicated health worker who used flip charts and interactive discussions. The RCT used the WHO simplified grading system (presence of TF and TI). The review reported that there was no significant difference in active trachoma between groups at 1 and 2 years (1 year: 39% with intervention *v* 34% with no intervention; 2 years: 54% with intervention *v* 49% with no intervention; absolute numbers not reported, P value not reported). [33] There was also no significant difference between groups in *C trachomatis* infection at 1 year (P = 0.39) or 2 years (P = 0.11). [33] However, the review noted that 3 months may have been too short for an educational intervention to have an effect, both groups received regular trachoma control messages on the radio, and the wells provided may have been inadequate for the size of the communities (1–3 wells per community of 600–1200 people). [33] It also reported that there was a significant difference between the groups at baseline in infection (*C trachomatis* infection: 26% with intervention *v* 14% with no intervention, P = 0.02), and children in the intervention villages were more likely to live in a compound with waste inside (70%) than children in control villages (51%; P value not reported). [33]

Harms:

Health education versus no intervention:
The review gave no information about harms. [33]

Health education plus improved water supply versus no intervention:
The review gave no information about harms. [33]

Comment:

A survey conducted in 2011 in two regions in Mali, where a radio messaging strategy (the National Blindness Prevention Program) had been used since 2008 to disseminate information about trachoma and its prevention, reported that 60% of people surveyed had heard information about trachoma on the radio. [39] A high proportion of people surveyed responded correctly to knowledge questions assessing understanding about the causes of trachoma, health impact, and prevention measures. Data for questions on behaviour included 66% claiming to wash their children's faces at least twice a day, and 94% reporting latrine disposal of faeces. Of those with positive responses to the knowledge and behaviour questions, 60% said that they had learned about trachoma and prevention measure from the radio messaging. However, there was no significant difference in the proportion of children with clean faces whose primary carers had heard the radio messaging compared with the proportion of clean faces in children whose primary carers had not heard the radio messaging.

GLOSSARY

Trichiasis The misdirection of lashes towards the eyeball.

Entropion Inversion of the eye lid.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Face washing alone One already reported systematic review updated. [27] Categorisation unchanged (unknown effectiveness).

Face washing plus topical antibiotics One already reported systematic review updated. [27] Categorisation unchanged (likely to be beneficial).

Fly control through the provision of pit latrines One already reported systematic review updated [33] with one RCT added. [34] One further report of an RCT added to Comment section. [35] Categorisation unchanged (unknown effectiveness).

Fly control using insecticide alone One already reported systematic review updated. [33] Categorisation unchanged (likely to be beneficial).

Fly control using insecticide plus mass antibiotic treatment One already reported systematic review updated. [33] Categorisation unchanged (unknown effectiveness).

Health education One already reported systematic review updated [33] with one RCT added. [38] Categorisation unchanged (unknown effectiveness).

Antibiotics One already reported systematic review updated [17] and one systematic review added. [18] Two RCTs added to the Comment section. [20] [21] Categorisation changed from 'unknown effectiveness' to 'likely to be beneficial'.

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TABLE **GRADE evaluation of interventions for trachoma**

Important outcomes	Prevalence of trachoma, adverse effects								
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of interventions to prevent scarring trachoma by reducing the prevalence of active trachoma?									
1 (457) [28] [29]	Prevalence of trachoma	Face washing *v* no intervention	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for uncertainty about disease definition, which may limit applicability of results
1 (523) [28] [29]	Prevalence of trachoma	Face washing plus topical tetracycline *v* no intervention	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for uncertainty about disease definition, which may limit applicability of results
2 (2103) [28] [29] [32]	Prevalence of trachoma	Promotion of face washing plus topical tetracycline *v* topical tetracycline alone	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for uncertainty about disease definition, which may limit applicability of results
2 (at least 7080) [12] [34]	Prevalence of trachoma	Fly control through the provision of household pit latrines *v* control	4	–1	0	–1	0	Low	Quality point deducted for weak methods; directness point deducted for co-intervention in 1 RCT (antibiotics)
2 (8004) [11] [12]	Prevalence of trachoma	Fly control using insecticide alone *v* no intervention	4	–2	0	0	0	Low	Quality points deducted for weak methods and incomplete reporting of results
1 (unclear) [33]	Prevalence of trachoma	Health education *v*no intervention	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods; directness point deducted for single village in analysis, restricting interpretation and generalisability
1 (unclear) [33]	Prevalence of trachoma	Health education plus improved water supply *v* no intervention	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and weak methods; directness point deducted for baseline differences between groups and possibly inadequate interventions restricting generalisability
At least 13 (at least 6306) [17]	Prevalence of trachoma	Antibiotic *v* placebo or no treatment	4	–1	–1	–1	0	Very low	Quality point deducted for weak methods; consistency point deducted for statistical heterogeneity; directness point deducted for clinically varied trials, limiting generalisability of results
At least 7 (at least 6955) [17]	Prevalence of trachoma	Oral antibiotics *v* topical antibiotics	4	–1	–1	–1	0	Very low	Quality point deducted for weak methods; consistency point deducted for statistical heterogeneity; directness point deducted for clinically varied trials, limiting generalisability of results

Type of evidence: 4 = RCT; 2 = Observational; 1 = Non-analytical/expert opinion. Consistency: similarity of results across studies
Directness: generalisability of population or outcomes
Effect size: based on relative risk or odds ratio